ARIPIPRAZOLE AND ATYPICAL NEUROLEPTIC MALIGNANT SYNDROME

To the Editor:

We report a case of atypical neuroleptic malignant syndrome (NMS) that developed within days of initiation of aripiprazole. To our knowledge, there are no published reports of NMS with aripiprazole.

NMS is a rare but potentially fatal iatrogenic condition that develops after the initiation of treatment with an antipsychotic drug. Classic features include muscle rigidity, autonomic instability, delirium, and hyperpyrexia. Additional manifestations may include elevated creatine phosphokinase, myoglobinuria, and acute renal failure (Caroff et al., 2000).

Atypical antipsychotics produce lower rates of extrapyramidal symptoms (EPS) relative to conventional antipsychotics and may be less likely to induce NMS. Inadequate control of EPS has been proposed as a risk factor for NMS (Primeau et al., 1987). Switching or discontinuation of antipsychotics may represent another risk factor (Caroff et al., 2000).

Aripiprazole has been described as a "dopamine system stabilizer" (Stahl, 2001) with a unique psychopharmacologic profile that may limit the development of hypodopaminergic states. Aripiprazole acts as an antagonist and partial agonist at dopamine D_2 receptors, a partial agonist at serotonin 5-HT_{1A} receptors, and an antagonist at 5-HT_{2A} receptors. Its mean elimination half-life is 75 hours. Clinical trials indicate that aripiprazole is effective in the treatment of schizophrenia and schizoaffective disorder and is well tolerated (Kane et al., 2002).

M is a 17-year-old African-American male with a history of paranoid schizophrenia who was hospitalized after acutely developing confusion and muscle rigidity. The onset of psychosis occurred 1 year ago, but he remained untreated until he was placed in a boys' training school 6 months ago. Medication trials of 4 to 8 weeks' duration included quetiapine 600 mg/day, olanzapine 20 mg/day, and ziprasidone 160 mg/day. Although all were discontinued for either lack of treatment response or side effects, no EPS were documented.

Within 3 days of starting aripiprazole 15 mg/day, M developed a shuffling gait, masked facies, and resting tremor. Despite discontinuing aripiprazole on day 6, his temperature was 99.0°F, with blood pressure of 140/104 mm Hg and pulse of 102 bpm. M continued to be "confused, unable to speak, drooling, and rigid" on day 8. Although there was mild improvement in his rigidity after 2 mg lorazepam orally, he continued to be described as "catatonic," prompting his referral to our Psychiatric Emergency Services.

There he was mute and exhibited "cogwheel rigidity and resting tremor." He was afebrile, yet his blood pressure was 149/105 mm Hg with a pulse of 102 bpm. Laboratory tests revealed elevated levels of creatine phosphokinase (762 IU/L), aspartate aminotransferase (47 IU/L), alanine aminotransferase (49 IU/L), and blood urea nitrogen (22 mg/dL). Benztropine 2 mg intramuscularly produced some mild relief of rigidity. With admission to the inpatient psychiatric unit, significant muscle rigidity, psychomotor slowing, confusion, inability to take nutrition, and psychotic symptoms were prominent. The treating psychiatrists and the pediatric neurology consultants concluded that the patient's clinical presentation was most consistent with early NMS. Symptomatic treatment with benztropine 4–6 mg/day and lorazepam 4 mg/day stabilized M's vital signs and laboratory measures. Within 4 days of admission, there was significant improvement in motor function, mental status, and self-care. Unfortunately, a residual state of confusion and psychosis persisted for several days. Electroconvulsive therapy was chosen to treat the patient's psychosis given the potential risk that a rechallenge with a neuroleptic would pose.

The presentation of NMS is heterogeneous. Atypical antipsychotics may tend to produce milder or atypical manifestations of NMS and have been found to be associated with less frequent extreme temperature elevations (Caroff et al., 2000).

This case prompts several questions. Given that M tolerated three previous trials of atypical antipsychotic medications, could he have been sensitized to the development of NMS? Would NMS have developed with the use of aripiprazole if M were neuroleptic naïve? What role did aripiprazole's long elimination half-life play in the progression of NMS despite its discontinuation?

This case is presented to alert clinicians of the potential for the development of NMS with aripiprazole. Despite its novel mechanism of action and reported safety, further studies are required to clarify its potential for the development of toxicity, including NMS.

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RISPERIDONE AND PANCREATITIS

To the Editor:

We report a case of risperidone-associated pancreatitis in a 7-year, 10-month-old boy. No infectious, traumatic, or other causes could be found by the pediatric and gastrointestinal services. Because he recently had been started on risperidone, it was determined that this was the likely cause of his pancreatitis.

The patient was a term baby, in breech position, delivered by cesarean section. His mother used methamphetamine during the first 2 months of pregnancy. He spent approximately 12 days in the neonatal intensive care unit after delivery. His psychiatric problems started to age 2 years and consisted of his being excessively hyperactive, easily agitated, cognitively delayed, and difficult for his single mother to manage. He was seen briefly around age 2 for mental health intervention. No psychiatric medications were tried at the time, but some behavioral interventions were suggested. He reportedly had a seizure disorder beginning in the first year of life and was treated with valproate and carbamazepine. These medications were well tolerated, with no history of pancreatitis. He has been seizure free and off all antiepileptic drugs since at least 4 years of age.

The patient was in his usual state of good physical health but was troubled emotionally and behaviorally when 6 weeks before hospital admission his mother brought him to see a child psychiatrist in their community. In the preceding weeks, he had become more oppositional, aggressive, and violent, having assaulted his 3-year-old brother. His mother also expressed concerns that he may also have been hearing voices. He began a trial of risperidone, 0.5 mg orally b.i.d., his first psychiatric medication intervention. He had a prompt response to risperidone, with decreased aggressive behavior, and his mother reported no further psychotic symptoms.

However, 4 weeks later (2 weeks before admission), he began complaining of periumbilical and left-sided abdominal pain, which was worse after eating and associated with vomiting several times daily. After 2 weeks of these gastrointestinal symptoms, he was diagnosed with pancreatitis and transferred to a university medical center for further evaluation and care. On the day of admission, he had abdominal tenderness to palpation without rebound or guarding, a temperature of 102°F, white blood cell count of 18,100/mm^3, hemoglobin/hematocrit of 12.3 g/dL/35.9%, platelet count of 657,000/mm^3, albumin of 2.8 g/dL, and lipase of 292 U. Amylase was 246 U/dL on hospital day 9.

He was made NPO, risperidone was stopped, and he was given ketorolac and morphine for pain relief. Abdominal computed tomography on hospital day 4 revealed a 9 × 5 × 7 cm fluid collection and a 4 × 4 cm multiloculated area adjacent to the pancreas. That same day, a pigtail catheter was placed in the pseudocyst for drainage. After 3 weeks of treatment, his drainage tube was removed. On hospital day 17, his white blood cell count was 5,700/mm^3, hemoglobin was 10.7 g/dL, hematocrit was 30.7%, platelets were 318,000/mm^3, and albumin was increased to 3.6. Amylase was maximal at 583 U/dL on hospital day 16 and decreased to 180 U/dL by discharge. Lipase reached a maximum of 1,290 U on hospital day 18 and decreased to 324 U by discharge. A repeat computed tomography scan on hospital day 19 showed improvement in the earlier demonstrated abnormalities. Oral feedings were started, tolerated with some difficulties initially, and he was discharged after 1 month in the hospital. During the inpatient stay, he did not exhibit psychosis or aggressive behavior. It was arranged for him to receive follow-up psychiatric care in his community after discharge.

Pancreatitis is a very serious illness, associated with substantial morbidity and potentially life-threatening complications. A study by Koller et al. (2003) in adult patients examined 192 cases of antipsychotic-associated pancreatitis with the antipsychotics haloperidol, risperidone, olanzapine, and clozapine. Twenty-two of the patients died. The rates of the specific antipsychotics in these cases were 40% with clozapine, 33% with olanzapine, 16% with risperidone, and 12% with haloperidol, suggesting a greater risk with the atypical agents. Individual cases of apparent risperidone-associated pancreatitis have been reported by Cordeiro and Elkis (2001) and Berent et al. (1997). In addition, there have been individual case reports of pancreatitis associated with

olanzapine (Doucette et al., 2000; Hagger et al., 2000; Ragucci and Wells, 2001), clozapine (Bergemann et al., 1999; Cerulli, 1999; Garlipp et al., 2002; Gatto et al., 1998; Jubert, 1994; Wehmeier et al., 2003), and ziprasidone (Yang, 2002). This case, like most other reported cases, occurred within the first 6 months of exposure. A PubMed search found no reported cases of risperidone in children. Given the increasing and widespread prescription of risperidone and the other atypical antipsychotic agents, not only for psychotic disorders but for mood disorders and disruptive behaviors as well, we thought that this report was noteworthy. Patients with exposure to risperidone who manifest abdominal pain need to have acute, drug-induced pancreatitis included in the differential diagnosis with prompt evaluation, and assessment of amylase and lipase levels needs to be considered. Although these agents are often extremely efficacious, careful evaluation and thoughtful biopsychosocial treatment planning remain necessary.

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